

Effects of Astragalus Mongholicus and Its Fermentation Objects on Anti-oxidation Capability of Hypothyroidism Rats

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Abstract: *Objectives:* The morbidity rate of hypothyroidism is relatively high, the features of which are deliquescent invasion, long course, atypical symptoms, great harm, etc. To intervene and cure hypothyroidism by traditional Chinese medicine could palliate untoward reaction of Western medicine, relieve symptoms of patients and enhance immunity. Astragalus mongholicus is frequently used as clinical traditional Chinese medicine. Reported by some literatures, compositions of Astragalus mongholicus have antioxidative function. Therefore, we studied effects of Astragalus mongholicus and its fermentation objects on anti-oxidation capability of hypothyroidism rats, and then discussed its mechanism of action. *Methods:* Eighty Wistar rats, half of which are female, were randomly divided into eight groups. They were named normal control group, hypothyroidism model group, high-dose Astragalus mongholicus group, medium-dose Astragalus mongholicus group, low-dose Astragalus mongholicus group, high-dose Astragalus mongholicus fermentation objects group, medium-dose Astragalus mongholicus fermentation objects group, low-dose Astragalus mongholicus fermentation objects group. There were ten rats in each group. We copied hypothyroidism rats samples by chemical induction-----0.05% PTU freely drinking water. The rats were treated by different doses of Astragalus mongholicus as well as its fermentation objects and killed after four weeks. We tested activity of serum superoxide dismutases (SOD), glutathion peroxidase (GSH-Px) nitricoxide synthase (NOS); contents of malondialdehyde (MDA), nitrogen monoxidum (NO) and the function of glandula thyroidea. *Results:* After being treated by Astragalus mongholicus as well as its fermentation objects, the hypothyroidism rats' function of glandula thyroidea has improved evidently ($P<0.05$). Secondly, contents of malondialdehyde (MDA) in blood serum degraded remarkably ($P<0.05$). Thirdly, activity of superoxide dismutases (SOD) and glutathione. Peroxidase (GSH-Px) in blood serum stepped up strikingly ($P<0.05$). Fourthly, vis vitalis of nitric oxide synthase (NOS) and contents of nitrogen monoxidum (NO) in blood serum stepped down surprisingly ($P<0.05$). *Conclusion:* Astragalus mongholicus and its fermentation objects have certain therapeutical effects on thyroid hypofunction, whose mechanism has something to do with increasing anti-oxidation capability of hypothyroidism rats.

Keywords: Astragalus Mongholicus and Its Fermentation Objects, Hypothyroidism Rats, Anti-oxidation Capability

1. Introduction

Hypothyroidism is a kind of endocrine secretion disease resulted from synthesis or secretion shortage of thyroid hormones and biological effect degrading, which is caused by hypothyroidism originating from multi-etiological factors. The attack rate of hypothyroidism is about five to ten percent [1] and the features of which are deliquescent invasion, long course, untypical symptoms and great harm [2]. According to decreasence degree of patients' thyroid glands, hypothyroidism can be divided into subclinical hypothyroidism (SCH) and clinical hypothyroidism. Hypothyroidism happens commonly among the elderly, especially senium female patients. The clinical representations mainly are chilly, debilitation, hyphidrosis, extremity engorgement, lethargy, insomnia, remembrance decreasence, ambulation disequilibrium, weight gain, constipation, pain of joints and muscles, etc [3]. In recent years, traditional Chinese medicine has seen comparatively noticeable curative effects on treating thyroid hypofunction because of its distinct advantages and exact functions. Using traditional Chinese medicine to intervene and treat hypothyroidism could mitigate adverse effects of Western medicine, lessen symptoms of patients and raise immunity [4, 5]. Astragalus mongholicus, whose components have antioxidative function according to documents and reports [6, 7], is commonly-used clinical traditional Chinese medicine. With the modernization development of traditional Chinese medicine, some studies show that fermentation objects of Astragalus mongholicus precipitated by microorganism fermentation can make effective ingredients of Astragalus mongholicus fully used [8]. Therefore, research on fermentation objects of Astragalus mongholicus has sense in theory and practice. Based on successfully replicating hypothyroidism rat models, our study was carried out. We fed the rats Astragalus mongholicus and its fermentation objects in different doses, observing antioxidative capabilities changes of hypothyroidism rats before and after administration. Accordingly, we approached its possible mechanism of action.

2. Data and Methods

2.1. Chief Materials and Reagents

Astragalus mongholicus, bought from Beijing Tongrentang Pharmaceutical Factory, was used to make Astragalus mongholicus extract [9] and Astragalus mongholicus fermentation extract [10]. Then the extracts were respectively prepared in three doses---low dose (0.25g/ml), medium dose (0.50g/ml), high dose (1.00g/ml). 0.1 percent suspension turbid fluid was prepared by isotonic Na chloride and PTU (from Shanghai Chaohui Pharmaceuticals, Batch number: 20181205). ELISA detection kits of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄), thyroid-stimulating hormone (TSH) were all purchased from Shanghai Yaji Biotechnology Company. Detection kits of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), nitricoxide synthase (NOS), nitrogen monoxidum (NO) were all bought from Nanjing

Jiancheng Institute of Biological engineering.

2.2. Main Equipments

Spectra MaxM4 full wavelength enzyme marker produced by American Molecule Company, Model Sigma 3K15 overdrive refrigerated centrifuge produced by Germany Sigma Company, Milli-Q Academic ultra-water purifier produced by American Millipore Company, SHA-B aqueous bath constant temperature oscillator produced by Changzhou Guohua Electrical Appliance Company Limited.

2.3. Creatures Grouping and Disposal

We chose eighty one-month ablactation Wistar rats (bought from Beijing Sibeifu Biotechnology Company Limited, experimental animal production license number: SCXK (Jing) 2016-0002), which weigh 180±10g, half of which are female. The rats were divided into eight groups randomly and averagely as normal control group, hypothyroidism model group, high-dose Astragalus mongholicus group, medium-dose Astragalus mongholicus group, low-dose Astragalus mongholicus group, high-dose Astragalus mongholicus fermentation objects group, medium-dose Astragalus mongholicus fermentation objects group, low-dose Astragalus mongholicus fermentation objects group. Slightly improved in accordance with PantosC Methods [11] and so on, hypothyroidism rats model was replicated. (experimental animal utilization license number: SYXK (Ji) 2019-006).

2.3.1. Model Building Method

We adopted chemical induction method. Model building group rats drank tap water containing 0.05% PTU while normal control rats were supplied with equal dose tap water. Four weeks later, thyroid gland function was detected.

2.3.2. Therapy Methods

Therapy began after successful model building. Administration dosage was adjusted according to weight each week. Astragalus mongholicus extracts were supplied respectively to rats of high-dose Astragalus mongholicus group, medium-dose Astragalus mongholicus group, low-dose Astragalus mongholicus group once a day for four weeks as 250mg/100g, 500mg/200g, 1000mg/100g. At the same time, Astragalus mongholicus fermentation object extracts were supplied respectively to rats of high-dose Astragalus mongholicus fermentation objects group, medium-dose Astragalus mongholicus fermentation objects group, low-dose Astragalus mongholicus fermentation objects group as 250mg/100g, 500mg/200g, 1000mg/100g. Meanwhile, distilled water of equal volume was given to rats of model group. The whole experiment lasted eight weeks. Blood was taken from femoral artery. Blood serum was segregated by 4°C 3000 r/min centrifugalization for fifteen minutes and then stored by refrigeration in the -80°C refrigerator.

2.4. Functional Examination of Thyroid Gland

To take fresh blood by bloodletting from femoral artery.

Blood serum was prepared and conserved in low temperature. We detected levels of FT₃, FT₄, TSH of blood serum of the rats with enzyme linked immunosorbent assay.

2.5. Detection of Anti-oxidation Capability

To take fresh blood by bloodletting from femoral artery. Blood serum was prepared and conserved in low temperature. We detected activity of SOD, activity of GSH-Px, vigor of NOS, content of NO, content of MDA, carrying out operation severely according to instructions of kits.

2.6. Statistical Method

Software SPSS17.0 was used for data analysis and management. All the data were expressed by ($\bar{x} \pm s$). One-factor analysis of variance was adopted in group comparison. $P < 0.05$ suggests that there was statistical significance.

3. Results

3.1. Effects of Astragalus Mongholicus and Its Fermentation Objects on Levels of FT₃, FT₄, TSH

Levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄), thyroid-stimulating hormone (TSH) of serum of normal control rats are all within normal limits, which shows euthyroidism. Compared with normal control, levels of

3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄) of serum of hypothyroidism model group rats were evidently lower while the level of thyroid-stimulating hormone (TSH) was significantly higher. And the difference was statistically significant ($P < 0.01$), which reflects hypothyroidism model was successfully copied. Compared with hypothyroidism model group, levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄) of serum of high-dose Astragalus mongholicus group and high-dose Astragalus mongholicus fermentation objects group rats were evidently higher. There was statistical significance over the difference ($P < 0.05$). Contribution of high-dose Astragalus mongholicus fermentation objects group was the best. Levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄) of serum of medium-dose Astragalus mongholicus group and medium-dose Astragalus mongholicus fermentation objects group rats were evidently higher. There was statistical significance over the difference ($P < 0.05$). There was no marked change on levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄) of serum of low-dose Astragalus mongholicus group and low-dose Astragalus mongholicus fermentation objects group rats. And the difference was not statistically significant ($P > 0.05$). Compared with hypothyroidism model group, levels of thyroid-stimulating hormone (TSH) of serum of Astragalus mongholicus and Astragalus mongholicus fermentation objects therapy group rats degraded ($P < 0.05$). (Table 1)

Table 1. Effects of Astragalus mongholicus and its fermentation objects on levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄), thyroid-stimulating hormone (TSH) of serum of hypothyroidism rats ($\bar{x} \pm s$, $n = 10$).

Groups	Doses (g·ml ⁻¹)	FT ₃ (Pmol·L ⁻¹)	FT ₄ (Pmol·L ⁻¹)	TSH (mIU/L)
normal control group		3.70±0.53	13.58±1.00	0.66±0.18
hypothyroidism model group		2.37±0.63**	4.16±1.21**	1.45±0.28**
high-dose Astragalus mongholicus group	1	3.42±0.42 ^{##}	12.30±1.98 ^{##}	1.23±0.13 [#]
medium-dose Astragalus mongholicus group	0.5	3.01±0.58 [#]	8.49±1.35 ^{##}	1.24±0.19
low-dose Astragalus mongholicus group	0.25	2.79±0.39	5.28±1.24	1.35±0.31
high-dose Astragalus mongholicus fermentation objects group	1	3.49±0.42 ^{##}	12.42±1.38 ^{##}	1.13±0.29 [#]
medium-dose Astragalus mongholicus fermentation objects group	0.5	3.19±0.74 [#]	9.71±1.25 ^{##}	1.19±0.18 [#]
low-dose Astragalus mongholicus fermentation objects group	0.25	3.02±0.76	5.62±1.81	1.33±0.42

Compared with normal control, ** $P < 0.01$; Compared with hypothyroidism model group, [#] $P < 0.05$, ^{##} $P < 0.01$

3.2. Effects on Activity of SOD, GSH-Px, NOS and Contents of MDA, NO

Compared with normal control, activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) was evidently lower ($P < 0.01$), while activity of nitric oxide synthase (NOS) was significantly higher ($P < 0.01$). On the other hand, contents of malondialdehyde (MDA), nitrogen monoxide (NO) were increased obviously ($P < 0.01$). And the difference was statistically significant. Compared with hypothyroidism model group, activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) of serum of high-dose Astragalus mongholicus group and high-dose Astragalus mongholicus fermentation objects group rats were evidently higher ($P < 0.01$), while activity of nitric oxide synthase (NOS) was significantly lower ($P < 0.01$). On the

other hand, contents of malondialdehyde (MDA), nitrogen monoxide (NO) were degraded obviously ($P < 0.01$). And the difference was statistically significant. Activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) of serum of medium-dose Astragalus mongholicus group and medium-dose Astragalus mongholicus fermentation objects group rats were evidently higher ($P < 0.05$), while activity of nitric oxide synthase (NOS) was significantly lower ($P < 0.05$). On the other hand, contents of malondialdehyde (MDA), nitrogen monoxide (NO) were degraded obviously ($P < 0.05$). And the difference was statistically significant. There was no marked change on activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), nitric oxide synthase (NOS) ($P > 0.05$) and contents of malondialdehyde (MDA), nitrogen monoxide (NO) ($P > 0.05$) of serum of low-dose Astragalus mongholicus group and low-dose Astragalus mongholicus

fermentation objects group rats. And the difference was not statistically significant ($P>0.05$). (Table 2, Table 3)

Table 2. Effects of Astragalus mongholicus and its fermentation objects on activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and content of malondialdehyde (MDA) of serum of hypothyroidism rats ($\bar{x} \pm s$, $n=10$).

Groups	Doses (g·mL ⁻¹)	SOD (U·mL ⁻¹)	MDA (nmol·mL ⁻¹)	GSH-Px (U·uL ⁻¹)
normal control group		269.30±4.02	5.53±0.20	10.23±0.52
hypothyroidism model group		243.06±6.38**	6.82±0.55**	7.73±0.58**
high-dose Astragalus mongholicus group	1	262.31±5.14 [#]	5.82±0.51 [#]	9.89±0.22 [#]
medium-dose Astragalus mongholicus group	0.5	252.35±8.10 [#]	6.31±0.29 [#]	8.76±0.37 [#]
low-dose Astragalus mongholicus group	0.25	245.08±9.68	6.75±0.39	8.15±0.36
high-dose Astragalus mongholicus fermentation objects group	1	267.42±3.04 [#]	5.56±0.22 [#]	9.96±0.46 [#]
medium-dose Astragalus mongholicus fermentation objects group	0.5	256.06±14.94 [#]	6.11±0.20 [#]	9.02±0.48 [#]
low-dose Astragalus mongholicus fermentation objects group	0.25	249.68±8.84	6.62±0.62	8.30±1.28

Compared with normal control, ** $P<0.01$; Compared with hypothyroidism model group, [#] $P<0.05$, [#] $P<0.01$

Table 3. Effects of Astragalus mongholicus and its fermentation objects on activity of nitric oxide synthase (NOS) and content of nitrogen monoxide (NO) of serum of hypothyroidism rats ($\bar{x} \pm s$, $n=10$).

Groups	Doses (g·mL ⁻¹)	NOS (U·mL ⁻¹)	NO (umol·L ⁻¹)
normal control group		12.61±1.47	14.16±0.52
hypothyroidism model group		15.51±2.25**	48.63±3.91**
high-dose Astragalus mongholicus group	1	13.23±2.02 [#]	25.32±2.21 [#]
medium-dose Astragalus mongholicus group	0.5	14.21±2.51	31.32±1.44 [#]
low-dose Astragalus mongholicus group	0.25	15.05±4.80	46.12±2.67
high-dose Astragalus mongholicus fermentation objects group	1	13.01±1.85 [#]	18.45±0.74 [#]
medium-dose Astragalus mongholicus fermentation objects group	0.5	13.93±3.03	28.52±0.95 [#]
low-dose Astragalus mongholicus fermentation objects group	0.25	14.70±3.67	44.37±4.14 [#]

Compared with normal control, ** $P<0.01$; Compared with hypothyroidism model group, [#] $P<0.05$, [#] $P<0.01$

4. Discussion

Hypothyroidism is a disease caused by degrading of thyroid hormone activity resulting from various factors. Thyroid hormones include 3,5,3'-triiodothyronine (FT₃) and free thyroxine (FT₄). Triiodothyronine and thyroxine exist in the ways of combination and dissociation. As the activity forms of triiodothyronine and thyroxine, 3,5,3'-triiodothyronine (FT₃) and free thyroxine (FT₄), whose levels are not influenced by concentration changes of thyroid binding globulin, can exactly reflect hormone levels of organisms [12, 13]. Levels of 3,5,3'-triiodothyronine (FT₃) and free thyroxine (FT₄) have positive correlation with function of thyroid gland, which is commonly used for clinical diagnosis index of thyroid disease [14]. Thyroid-stimulating hormone (TSH) is thyroid-stimulating hormone which is in charge of regulating production and secretion of thyroid hormone, secreted and generated by adenohypophysis. Under the state of hypothyroidism, levels of triiodothyronine and thyroxine in vivo are degraded obviously, which promotes secretion of thyroid-stimulating hormone (TSH) through the negative feedback mechanism of hypothalamus to hypophysis to thyroid gland axle. When hypothyroidism happens, levels of thyroid-stimulating hormone (TSH) in the blood serum rise abnormally, which is used as index to reflect function of thyroid gland [15]. Our findings show that levels of 3,5,3'-triiodothyronine (FT₃), free thyroxine (FT₄) of serum of hypothyroidism model group rats were evidently lower. That

is to say, levels of thyroid hormone were degraded strikingly, leading to metabolic disorder of thyroid. Levels of thyroid-stimulating hormone (TSH) were significantly higher, which indicates that function of thyroid was damaged. Astragalus mongholicus and its fermentation objects can make levels of thyroid hormone of serum of the rats increased evidently as well as degrading levels of thyroid-stimulating hormone (TSH), which indicates that Astragalus mongholicus extract and Astragalus mongholicus fermentation extract can equally improve function of thyroid to play the role of therapy. Furthermore, function and effect of Astragalus mongholicus's fermentation objects is the best.

Degrading of activity of thyroid hormone can result in enhancement of oxidative stress in the organism [16]. Excess oxygen free radicals in the organism can cause oxidative damage which happens in biomacromolecules. As is known to all, superoxide dismutase (SOD) is one of the most important antioxidants in vivo. It is in the first line of defense to remove reactive oxygen species (ROS), which has very crucial effects to get rid of oxygen free radicals and prevent molecule damage caused by oxygen free radicals. Superoxide dismutase (SOD) can even protect glutathione peroxidase (GSH-Px) and catalase (CAT) against deactivation effects of oxygen free radicals. Amount of malondialdehyde (MDA) in the human body can reflect degree of lipid peroxidation and accordingly reflect degree of histiocyte damage indirectly. Glutathione peroxidase (GSH-Px), together with superoxide dismutase (SOD) and catalase (CAT), with glutathione being substrate, removes active oxygen in vivo, degrading levels hydrogen

dioxide, lessening and preventing peroxidization of active oxygen, eliminating levels of malondialdehyde (MDA) which is product of lipid peroxidation [17-18]. Nitrogen monoxidum (NO), which inhibits activity of nitricoxide synthase (NOS), is a product catalyzed by nitricoxide synthase (NOS) and can decrease producing of free radicals [19]. Nitrogen monoxidum (NO) is a kind of phlegmasia nature mediator and an important marker to monitor level of inflammation [20]. Our findings show that compared with normal control, activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) was evidently lower while contents of malondialdehyde (MDA) were increased obviously, which indicates that oxidative damage happened in vivo of hypothyroidism rats. Astragalus mongholicus and its fermentation objects can make activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) of serum of hypothyroidism rats rise and contents of malondialdehyde (MDA) degrade. Compared with normal control, activity of nitricoxide synthase (NOS) of serum of hypothyroidism rats step up obviously and contents of nitrogen monoxidum (NO) increase remarkably. Possibly oxidative stress induced the occurrence of inflammatory reaction. Astragalus mongholicus and its fermentation objects can make activity of nitricoxide synthase (NOS) of serum of hypothyroidism rats and contents of nitrogen monoxidum (NO) degrade, which indicated that Astragalus mongholicus and its fermentation objects can protect hypothyroidism rats against damage of oxidative stress and inhibit inflammatory reaction induced by oxidative stress.

Hypothyroidism belongs to the category of deficiency exhaustion, hydroncus, etc. in Traditional Chinese Medicine. The chief clinical manifestations are symptoms of yang asthenia and exhaustion of qi, such as lack of healthy energy, insufficiency of vital energy and blood, etc. including body tiredness and weakness, no warmth of limbs, lazy speech and hypologia, and so on [21]. Astragalus mongholicus is classified as the pulse family and milk vetch, which contains many kinds of active constituents such as flavonoids, polysaccharoses, etc. It is clinically commonly used traditional Chinese drug, which has long history [22, 23]. Astragalus mongholicus has the effects such as invigorating vital energy and supporting blood, strengthening the middle warmer and benefiting vital energy, inducing diuresis to alleviate edema, etc. Astragalus mongholicus is used to improve healthy energy loss and insufficiency of vital energy and blood of patients, which accordingly relieves symptoms of hypothyroidism, through its effects of invigorating the spleen, invigorating vital energy, enriching the blood, etc. Astragalus mongholicus has certain therapeutic efficacy to hypothyroidism. Contemporary studies show that Astragalus mongholicus has extensive pharmacologic action of adjusting immunity, antioxygen, etc [24, 25].

5. Conclusion

To sum up, Astragalus mongholicus made and adopted through different processes in our project was used to

intervene hypothyroidism rats. To be specific, rats of hypothyroidism model were cured by extracts of Astragalus mongholicus and its fermentation objects in different doses. Then we determined indexes of thyroid gland and oxidative stress of hypothyroidism rats before and after therapy. We found that function of thyroid gland of post-treatment was reinforced as well as activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) was heightened. However, contents of malondialdehyde (MDA) of post-treatment degraded compared to prior therapy. It turned out that Astragalus mongholicus and its fermentation objects have the effect of enhancing antioxidative capability of hypothyroidism rats. It improved function of thyroid gland and effects of Astragalus mongholicus's fermentation objects were the best. The initial discussion of possible mechanism of Astragalus mongholicus and its fermentation objects to treat hypothyroidism is to offer more bases in theory and thoughts for clinical prevention and cure of hypothyroidism and then better guide clinical practice. However, because the condition of our study was limited, its mechanism of action needs further research.

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